CHEST Online Supplement

A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults

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CHEST 2017; 152(4):712-722

 DOI: 10.1016/j.chest.2017.03.061

e-Appendix 1.

SUPPLEMENTAL METHODS

A. Characteristics of the Study Intensive Care Units

Characteristic	Vanderbilt	LSU	Oschner	UAB
Annual admissions	3,800	2,880	3,500	2,000
ICU beds	34	38	33	24
ICU type	medical	medical, cardiac, neuro	medical	medical
Number of clinical PCCM fellows	12	13	13	15
Personnel present at intubation				
PCCM or anesthesia attending	Always	Always	Always	Sometimes
PCCM fellow	Always	Always	Always	Always
Respiratory therapist	Always	Always	Always	Always
Bedside nurse	Always	Always	Always	Always
Charge nurse	Almost always	Sometimes	Sometimes	Almost Always
Resident or nurse practitioner	Often	Always	Often	Often
Airway supplies stored in the ICU				
Airway bag or box	Yes	Yes	Yes	Yes
Direct laryngoscope	Yes	Yes	Yes	Yes
Video laryngoscope				
McGRATH® MAC	Yes	No	No	No
GlideScope® GVL	Yes	No	Yes	Yes
Storz C-MAC®	No	Yes	No	Yes
End-tidal CO_2 detector	Yes	Yes	Yes	Yes
Endotracheal tube introducer	Yes	Yes	Yes	Yes
Laryngeal mask airways	Yes	Yes	Yes	Yes
Cricothyrotomy kit	Yes	Yes	Yes	Yes
Hospital bed	Stryker® inTouch™	Stryker® inTouch™	Stryker® inTouch™	Hill-Rom® TotalCare P1900™
Monitoring				
Continuous heart rate	Always	Always	Always	Always
Non-invasive blood pressure	Always	Always	Always	Always
Invasive blood pressure	Rarely	Rarely	Rarely	Sometimes
Continuous oxygen saturation	Always	Always	Always	Always

Written pre-intubation Checklist*	Randomized	Randomized	Randomized	Present
Pre-medication				
Lidocaine	Rarely	Never	Never	Rarely
Atropine	Never	Never	Never	Never
Cricoid pressure	Rarely	Rarely	Rarely	Rarely
Apneic oxygenation	Rarely	Never	Never	Rarely
Endotracheal tube stylet	Always	Always	Always	Always
Post-intubation chest radiograph	Almost always	Always	Always	Always
IRB Number	150897	9092	2016.069	F151216004

Vanderbilt is Vanderbilt University Medical Center; LSU is Louisiana State University; Oschner is Ochsner Medical Center; UAB is University of Alabama at Birminghma; ICU is intensive care unit; PCCM is Pulmonary and Critical Care Medicine; IRB is institutional review board.

*In an additive factorial design[1], each patient enrolled at the Vanderbilt, LSU, and Oschner study sites was randomly assigned to ramped vs sniffing position (1:1 ratio) and to use of a written pre-intubation checklist vs usual care (1:1 ratio). At the UAB study site, a written pre-intubation checklist was in routine use prior to the current study and study group assignment controlled only patient position.

B. Bed Positioning in Each Study Group

RAMPED POSITION - For patients assigned to ramped position, the electronic bed controls (shown below for the Stryker® inTouch™ bed) were used to elevate the head of the bed to 25 degrees above horizontal, keeping the lower half of the bed parallel to the floor.

SNIFFING POSITION - For patients assigned to sniffing position, the electronic bed controls were used to ensure the entire bed was parallel to the floor.

C. Patient Positioning Study Materials

The following written descriptions of each position were available to operators online throughout the course of the trial:

RAMPED POSITION -- The patient will be moved toward the head of the bed until the head and neck are resting on the edge of the mattress. Keeping the lower half of the bed flat, the head of the bed will be raised to an angle of 25°. The patient's face will be parallel to the ceiling with neck in slight extension, torso at 25°, and legs parallel to the ceiling. Pillows and/or towels under the head will be added or removed as needed to achieve alignment of the external auditory meatus with the sternal notch. Once desired patient positioning is achieved the entire bed will be moved up or down to place the patient's mouth at a comfortable level for the fellow performing the procedure.

SNIFFING POSITION -- With the entire bed flat, pillows and/or blankets will be placed under the patient's head and/or neck. Initially, a goal of 7cm of head elevation will be targeted with the goal of flexion of the neck at 35° relative to the torso and head extension to position the face at a 15° angle to the ceiling. Pillows and/or blankets will be added or removed as needed to achieve alignment of the external auditory meatus and the sternal notch.

Notes:

1. Study protocol dictated only patient position during intubation and use of a written pre-intubation checklist. Decisions regarding the need for intubation, approach to pre-oxygenation, selection of medications, and choice of airway management equipment were made by the clinical team.
2. A stepstool was available when required to align the operator and the level of the patient's head after making adjustments to the level of the bed.
3. Prior studies in which the hospital bed, specialized devices, or towels were used to elevate the patient's torso and head in preparation for endotracheal intubation have used the following terminology to refer to this patient position: "Ramp" or "Ramped" position[2–5], "30 degree Back Up Fowler"[6], "Back-up Head-elevated position"[7], "25 degree back-up position"[8], "Head-elevated laryngoscopic position (HELP)"[2,9], "25 degree head-up"[10,11], and "20 degree head up tilt"[12].

D. Patient Positioning in Usual Care

In order to quantitate the use of sniffing position and ramped position during endotracheal intubation as part of usual ICU care during the time-period in which the trial was being conducted, we recorded observational data on patient positioning for consecutive intubations in the medical and neurological ICUs of a separate academic medical center not enrolling in the current trial (Harborview Medical Center, University of Washington, Seattle; IRB#51185). Among 32 consecutive ICU intubations for which clinical providers selected the patient's position, the sniffing or supine position was used for 12 (37.5%) intubations and the ramped position was used for 20 (62.5%) intubations. The median angle of the head of the bed when the provider used sniffing or supine position was 0 [IQR 0 – 7] degrees compared with 20 [IQR 19 – 24] degrees when the provider used ramped position.

E. Secondary and Tertiary Outcomes

Secondary oxygenation outcomes included incidence of hypoxemia (SpO2 < 90%), severe hypoxemia (SpO2 < 80%), desaturation (an absolute decrease in SpO2 greater than 3%), and absolute change in saturation from baseline.

Secondary procedural outcomes included Cormack-Lehane grade of glottic view[13], number of laryngoscopy attempts, time from induction to successful intubation, operator-reported difficulty of intubation, need for additional airway equipment or operators, need for patient repositioning during the procedure, incidence of aspiration, esophageal intubation, and airway trauma.

Secondary physiologic outcomes included lowest systolic blood pressure between induction and two minutes after intubation, incidence of systolic blood pressure less than 65 mmHg or new receipt of a vasopressor between induction and two minutes after intubation, and cardiac arrest within ten minutes of intubation.

Tertiary outcomes included ventilator-free days, ICU-free days, and in-hospital mortality.

F. Power Calculation

INITIAL SAMPLE SIZE CALCULATION (6/24/15):

As previous studies have shown that the standard deviation of the lowest oxygen saturation is 10% and a clinically meaningful difference between groups would be 5%, we will have to randomize a total of 170 airway events to give us 90% power at an alpha level of 0.05 to detect this difference.

REVISED SAMPLE SIZE CALCULATION (3/24/16):

Our initial sample size calculation utilized an anticipated standard deviation in lowest arterial oxygen saturation of 10% based on previous studies in critically ill adults. How accurately this estimate would represent the observed standard deviation in our study population carried considerable uncertainty. Therefore, after six months of enrollment in the current CHECK-UP trial, we evaluated the standard deviation for the lowest arterial oxygen saturation for all patients enrolled, with group assignments concealed. The observed standard deviation in the first six months of the current trial was 14%, significantly higher than the predicted 10%. In order to preserve adequate power we re-calculated a larger sample size. Using the observed standard deviation of 14% and a clinically meaningful difference in lowest arterial oxygen saturation between groups of 5%, maintaining 80% statistical power at an alpha level of 0.05 would require a total of 248 patients. Anticipating a low rate of missing data for the primary outcome, we selected a final sample size of 260 total patients.

Notes:

1. The revised sample size calculation was performed using the *standard deviation* for the primary outcome for the *overall study population*. At no point during enrollment were the *values* for the primary outcome evaluated, either overall or by group.
2. All sample size calculations were performed in the PS power and sample size program[14].
3. The trial was registered online prior to initiation (NCT02497729) and the statistical analysis plan was made available prior to the completion of enrollment[15].

G. Multivariable Modeling

We performed linear regression modeling of the relationship between group assignment and the primary outcome after accounting for oxygen saturation at the time of induction (model 1); oxygen saturation at the time of induction, age, body mass index, Acute Physiology and Chronic Health Evaluation (APACHE) II score, highest FiO2 in the prior 6 hours, use of a video laryngoscope, and operator prior intubating experience (model 2); or all of the above covariates plus a cross-product interaction term between group assignment and body mass index (model 3).

SUPPLEMENTAL TABLES

e-Table 1. Chronic comorbidities.

	Sniffing Position	**Ramped Position**
Comorbidity	**(n = 130)**	**(n = 130)**
Respiratory conditions, No. (%)		
Chronic obstructive pulmonary disease	25 (19.2)	29 (22.3)
Obstructive sleep apnea	11 (8.5)	15 (11.5)
Asthma	10 (7.7)	11 (8.5)
Pulmonary embolism	8 (6.2)	7 (5.4)
Lung cancer	5 (3.8)	7 (5.4)
Chronic respiratory infection	5 (3.8)	5 (3.8)
Interstitial lung disease	5 (3.8)	3 (2.3)
Cystic fibrosis	2 (1.5)	2 (1.5)
Neuromuscular disease	1 (0.8)	3 (2.3)
Recurrent aspiration	2 (1.5)	1 (0.8)
Non-cystic fibrosis bronchiectasis	0 (0.0)	2 (1.5)
Other*	14 (10.8)	6 (4.6)
Non-respiratory conditions, No.(%)		
Congestive heart failure	12 (9.2)	20 (15.4)
Coronary artery disease	18 (13.8)	23 (17.7)
Hypertension	57 (43.8)	54 (41.5)
Diabetes mellitus	32 (24.6)	33 (25.4)
Atrial fibrillation	7 (5.4)	16 (12.3)
Chronic kidney disease	11 (8.5)	9 (6.9)
Extra-pulmonary malignancy	33 (25.4)	25 (19.2)
Cirrhosis	30 (23.1)	26 (20.0)
Human immunodeficiency virus	4 (3.1)	6 (4.6)
Other	50 (38.5)	50 (38.5)

*Other chronic respiratory comorbidities observed included: hepatic hydrothorax, obesity hypoventilation syndrome, lung transplantation, pneumothorax requiring wedge resection, sarcoidosis, trapped lung, central hypoventilation, hepatopulmonary syndrome, bronchiolitis obliterans syndrome, tracheoesophageal fistula

e-Table 2. Active medical conditions at the time of intubation.

	Sniffing Position	Ramped Position
Condition, No. (%)	**(n = 130)**	**(n = 130)**
Sepsis	58 (44.6)	58 (44.6)
Septic shock	39 (30.0)	40 (30.8)
Cardiogenic shock	5 (3.8)	3 (2.3)
Non-sepsis distributive shock	3 (2.3)	2 (1.5)
Hemorrhagic shock	5 (3.8)	9 (6.9)
Gastrointestinal bleeding	24 (18.5)	23 (17.7)
Altered mental status	52 (40.0)	56 (43.1)
Hepatic encephalopathy	22 (16.0)	19 (14.6)
Stroke	0 (0.0)	3 (2.3)
COPD exacerbation	7 (5.4)	6 (4.6)
Asthma exacerbation	0 (0.0)	2 (1.5)
Pneumonia	38 (29.2)	48 (36.9)
Acute respiratory distress syndrome	15 (11.5)	16 (12.3)
Pulmonary embolism	4 (3.1)	0 (0.0)
Myocardial infarction	4 (3.1)	5 (3.8)
Cardiogenic pulmonary edema	7 (5.4)	11 (8.5)
Aspiration	9 (6.9)	9 (6.9)
Other	46 (35.4)	41 (31.5)

e-Table 3. Complete list of indications for endotracheal intubation.

	Sniffing Position	Ramped Position
Indication*, No. (%)	**(n = 130)**	**(n = 130)**
Hypoxemic respiratory failure	75 (57.7)	77 (59.2)
Hypercarbic respiratory failure	20 (15.4)	20 (15.4)
Altered mental status	48 (36.9)	46 (35.4)
Seizure	2 (1.5)	2 (1.5)
Upper airway compromise	4 (3.1)	3 (2.3)
Acidosis	7 (5.4)	6 (4.6)
Hemodynamic instability	8 (6.2)	18 (13.8)
Respiratory arrest	2 (1.5)	2 (1.5)
Agitation	0 (0.0)	1 (0.8)
Pre-procedural	17 (13.1)	17 (13.1)
Other	1 (0.8)	0 (0.0)

*Patients could have more than one indication for endotracheal intubation

e-Table 4. Difficult airway characteristics and MACOCHA score.

	Sniffing Position	Ramped Position
Difficult airway characteristics*, No. (%)	**(n = 130)**	**(n = 130)**
One or more difficult airway characteristic	55 (42.3)	58 (44.6)
BMI > 30 kg/m^2	44 (33.8)	40 (30.8)
Obstructive sleep apnea	11 (8.5)	15 (11.5)
Upper gastrointestinal bleeding	5 (3.8)	6 (4.6)
Limited mouth opening†	4 (3.1)	5 (3.8)
Limited neck mobility†	2 (1.5)	6 (4.6)
Witnessed aspiration	4 (3.1)	3 (2.3)
Airway mass or infection	3 (2.3)	2 (1.5)
Epistaxis or oral bleeding	1 (0.8)	0 (0.0)
Head or neck radiation	1 (0.8)	0 (0.0)
MACOCHA score‡	**(n = 57)**	**(n = 59)**
Total score, median [IQR]	2 [1-7]	3 [1-6]
Individual elements, No. (%)		
Mallampati score III or IV	22 (38.6)	19 (32.2)
Obstructive sleap apnea	13 (22.8)	18 (30.5)
Reduced mobility of cervical spine	1 (1.8)	1 (1.7)
Limited mouth opening <3cm	11 (19.3)	7 (11.9)
Coma	13 (22.8)	8 (13.6)
Severe hypoxemia (<80%)	3 (5.3)	2 (3.4)
Non-anesthesiologist operator	57 (100.0)	59 (100.0)

*Patients could have more than one difficult airway characteristic. Difficult airway characteristics were assessed for all 260 patients by study personnel via chart review for body mass index (BMI), pre-existing diagnosis of obstructive sleep apnea syndrome and prior head or neck radiation, and active upper gastrointestinal bleeding, aspiration, airway mass or infection, or epistaxis or oral bleeding at the time of induction.
†Limited mouth opening and limited neck mobility were reported by the operator after performing the procedure.
‡MACOCHA refers to the "Mallampati score III or IV, Apnea syndrome (obstructive), Cervical spine limitation, Opening mouth < 3 cm, Coma, Hypoxia, Anesthesiologist nontrained" score which predicts difficulty of endotracheal intubation in the intensive care unit on a scale from 0 (easy) to 12 (very difficult). Values for the MACOCHA score were calculated immediately prior to induction for those patients randomized to a written pre-intubation checklist as part of the factorialized design. Data on Mallampati score, presence of obstructive sleep apnea, reduced cervical spine mobility and limited mouth opening were based on the best information available to the operator prior to initiating the procedure.

e-Table 5. Pre-laryngoscopy management.

Characteristic	Sniffing Position (n = 130)	Ramped Position (n = 130)	*P* Value
Induction medication*, No. (%)			
Etomidate	114 (87.7)	120 (92.3)	.22
Ketamine	10 (7.7)	9 (6.9)	.81
Propofol	6 (4.6)	2 (2.3)	.50
Midazolam	2 (1.5)	4 (3.1)	.68
Neuromuscular blockade*, No. (%)			
Succinylcholine	62 (47.7)	69 (53.1)	.39
Rocuronium	64 (49.2)	58 (44.6)	.46
Vecuronium	0 (0.0)	0 (0.0)	>.99
Cisatracurium	0 (0.0)	0 (0.0)	>.99
None	4 (3.1)	3 (2.3)	>.99
Ventilation between induction and laryngoscopy*, No. (%)			
None	65 (50.0)	59 (45.4)	.46
Bag-valve-mask	48 (36.9)	55 (42.3)	.38
BIPAP	20 (15.4)	15 (11.5)	.36
Other	0 (0.0)	2 (1.5)	>.50
Laryngoscope used for first attempt, No. (%)			.88
Direct laryngoscope	97 (74.6)	98 (75.4)	
McGRATH® MAC video laryngoscope	20 (15.4)	19 (14.6)	
GlideScope® GVL video laryngoscope	9 (6.9)	7 (5.4)	
KARL STORZ C-MAC® video laryngoscope	4 (3.1)	6 (4.6)	
Curved laryngoscope blade, No. (%)	113 (86.9)	116 (89.2)	.57
Size of the laryngoscope blade, median [IQR]	4 [3-4]	4 [3-4]	.93
Endotracheal tube size, median [IQR]	8 [7.5-8]	8 [7.5-8]	.15

*Patients could receive more than one.

e-Table 6. Additional procedural and physiologic outcomes.

	Sniffing Position (n = 130)	Ramped Position (n = 130)	*P* Value
Cormack-Lehane grade of view*, No. (%)			.01
Grade I	63 (48.5)	61 (46.9)	
Grade II	52 (40.0)	36 (27.7)	
Grade III	14 (10.8)	27 (20.8)	
Grade IV	1 (0.8)	6 (4.6)	
Difficulty of intubation†, No. (%)			.04
Easy	105 (80.8)	88 (67.7)	
Moderate	18 (13.8)	26 (20.0)	
Difficult	6 (4.6)	16 (12.3)	
Unknown	1 (0.8)	0 (0.0)	
Number of laryngoscopy attempts, No. (%)			.02
One attempt	111 (85.4)	99 (76.2)	
Two attempts	16 (12.3)	21 (16.2)	
Three attempts	2 (1.5)	7 (5.4)	
Four or more attempts	1 (0.8)	3 (2.3)	
Time from induction to secured airway, median [IQR], seconds	110 [75-157]	119 [81-214]	.09
mean ± SD	140 ± 117	182 ± 184	
Intubation requiring 3 or more attempts or greater than 10 minutes‡, No. (%)	3 (2.3)	11 (8.5)	.05
Endotracheal tube introducer used, No. (%)	8 (6.2)	25 (19.2)	.002
Second laryngoscope type required, No. (%)	8 (6.2)	21 (16.2)	.01
Switch from direct to video, No.	8	17	
Switch from video to direct, No.	0	4	
Laryngeal mask airway required, No. (%)	0 (0.0)	1 (0.8)	>.99
Second operator required, No. (%)	1 (0.8)	4 (3.1)	>.37
Repositioning after induction required, No. (%)	4 (3.1)	9 (6.9)	.25
Procedural complications, No. (%)			
Lowest oxygen saturation < 70%‡	19 (15.0)	12 (9.4)	.18
Aspiration	1 (0.8)	2 (1.5)	>.99
Esophageal intubation	6 (4.6)	6 (4.6)	>.99
Airway trauma	0 (0.0)	0 (0.0)	>.99
Cardiac arrest	4 (3.1)	3 (2.3)	>.99
Heart rate < 40 beats per minute	2 (1.5)	1 (0.8)	>.99
Systolic blood pressure < 65 mmHg or new or increased vasopressor	25 (19.2)	25 (19.2)	>.99
New or increased vasopressor	24 (18.5)	24 (18.5)	>.99
Fluid bolus administered	15 (11.5)	11 (8.5)	.41
Endotracheal tube malposition on post-procedure chest radiograph, No. (%)	16 (12.5)	17 (13.2)	.87

*The Cormack-Lehane system classifies views obtained by direct laryngoscopy based on the structures seen with higher grades indicating more limited view.
†Difficulty of the intubation was subjectively assessed and reported by the operator.
‡Outcome added *post hoc*.

e-Table 7. Multivariable models for lowest oxygen saturation relative to study group.

Model 1	**Effect**	**95% Confidence interval**	***P* Value**
Ramped position	1.53	-1.59 – 4.65	.33
Saturation at induction, %	12.81	9.18 – 16.43	<0.001
Model 2	**Effect**	**95% Confidence interval**	***P* Value**
Ramped position	1.61	-1.55 – 4.76	.32
Saturation at induction, %	12.53	8.64 – 16.42	<0.001
Age (years)	2.37	0.39 – 4.34	.02
Body mass index (kg/m^2)	-1.14	-2.92 – 0.64	.21
APACHE II score	0.20	-1.91 – 2.31	.85
Highest FiO_2 in prior 6 hours	0.04	-4.04 – 4.12	.98
Video laryngoscope	-2.22	-5.94 – 1.50	.24
Operator experience	1.35	-0.63 – 3.34	.18
Model 3*	**Effect**	**95% Confidence interval**	***P* Value**
Ramped position	2.93	-1.01 – 6.87	.24
Body mass index (kg/m^2)	-1.33	-4.57 – 1.92	.10
Ramped*BMI interaction			.18
Saturation at induction, %	11.99	8.10 – 15.88	<0.001
Age (years)	2.47	0.48 – 4.46	.02
APACHE II score	0.12	-1.98 – 2.22	.91
Highest FiO_2 in prior 6 hours	-0.43	-4.54 – 3.67	.83
Video laryngoscope	-2.21	-5.93 – 1.51	.24
Operator experience	1.40	-0.57 – 3.38	.16

In multivariable linear regression models adjusting for oxygen saturation at the time of induction (model 1), additional pre-specified baseline confounders (model 2), and the interaction between body mass index (BMI) and study group assignment adjusting for baseline confounders (model 3), use of ramped positioning compared with sniffing position did not impact the mean lowest oxygen saturation. The difference in lowest arterial oxygen saturation (%) is given for ramped position relative to sniffing position, video relative to direct laryngoscopy, and the 75th percentile relative to the 25th percentile of saturation at induction, age, body mass index, APAHCE II score, highest FiO_2 in the prior 6 hours, and the operator's number of prior intubations.

*In a *post hoc* analysis in which the interaction term between study group assignment and BMI in model 3 was replaced by an interaction term between study group assignment and "use of bilevel positive airway pressure or bag-valve-mask ventilation for preoxygenation" as a categorical variable, there was no interaction between group assignment and preoxygenation method (*P* value for interaction = .91). Among the 116 patients for whom bilevel positive airway pressure or bag-valve-mask ventilation was used for preoxygenation, the median lowest arterial oxygen saturation was 92% [IQR 80 – 98] in the sniffing position group (n=57) and 93% [IQR 85 – 99] in the ramped position group (n=59) (*P* = .42).

APACHE II = Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness

FiO_2 in prior 6 hours = highest fraction of inspired oxygen in the 6 hours prior to intubation

e-Table 8. Protocol Violations

	Patient 1	Patient 2	Patient 3
Administrative Information			
Months since starting enrollment	1	7	8
Position assigned	Ramped	Ramped	Sniffing
Position received	Sniffing	Sniffing	Ramped
Reason for violation recorded	Yes*	Yes†	Yes‡
Patient Characteristics			
Age (years)	60	71	77
Gender	Male	Male	Male
Body Mass Index (kg/m^2)	27.1	22.4	28.6
APACHE II score	34	26	21
BiPAP use in prior 6 hours	No	No	No
Highest FiO_2 in prior 6 hours	0.60	0.21	0.21
Lowest saturation in prior 6 hours	84	91	93
Operator Characteristics			
Number of prior intubations	7	39	15
Months of fellowship training	1.7	19.7	8.4
Procedural Characteristics			
Oxygen saturation at induction, %	90	98	100
Lowest oxygen saturation, %	82	85	100
Laryngoscopy device used	Direct	Direct	Direct
Cormack-Lehane grade of view	Grade 2	Grade 3	Grade 2
Difficulty of Intubation	Easy	Moderate	Moderate
Number of laryngoscopy attempts	1	1	1
Time to intubation (sec)	66	148	64

Raw data are presented for the three patients who were not intubated in the assigned position. APACHE = Acute Physiology and Chronic Health Evaluation II – ranging from 0 to 71 with higher scores indicating higher severity of illness; BiPAP = Bilevel Positive Airway Pressure; FiO_2 = fraction of inspired oxygen; Direct = direct laryngoscopy.
* "Patient changed to sniffing position prior to induction as would not remain in ramped position"
† "Rheumatoid arthritis patient whose neck didn't tolerate the ramped position so we had to move to sniffing position"
‡ "Had been in ramped position while preparing for intubation and accidently kept in ramped position for induction and laryngoscopy"

e-Table 9. Per-protocol analysis.

	Received Sniffing Position	Received Ramped Position	
Procedural characteristics	**(n = 131)**	**(n = 129)**	***P* Value**
Cormack-Lehane grade of view, No. (%)			.02
Grade I	63 (48.1)	61 (47.3)	
Grade II	52 (39.7)	36 (27.9)	
Grade III	15 (11.5)	26 (20.2)	
Grade IV	1 (0.8)	6 (4.7)	
Difficulty of intubation, No. (%)			.03
Easy	106 (80.9)	87 (67.4)	
Moderate	18 (13.7)	26 (20.2)	
Difficult	6 (4.6)	16 (12.4)	
Unknown	1 (0.8)	0 (0.0)	
Number of laryngoscopy attempts, No. (%)			.02
One attempt	112 (85.5)	98 (76.0)	
Two attempts	16 (12.2)	21 (16.3)	
Three attempts	2 (1.5)	7 (5.4)	
Four or more attempts	1 (0.8)	3 (2.5)	
Oxygenation outcomes			
Lowest oxygen saturation, median [IQR], %	91 [79-98]	93 [84-100]	.14
Lowest oxygen saturation < 90% No. (%)	55 (43.0)	48 (38.1)	.43
Lowest oxygen saturation < 80% No. (%)	36 (28.1)	26 (20.6)	.17
Decrease in oxygen saturation, median [IQR], %	4.0 [0.0-15.0]	3.0 [0.0-13.0]	.23
Decrease in oxygen saturation > 3% No. (%)	67 (52.8)	60 (47.6)	.41

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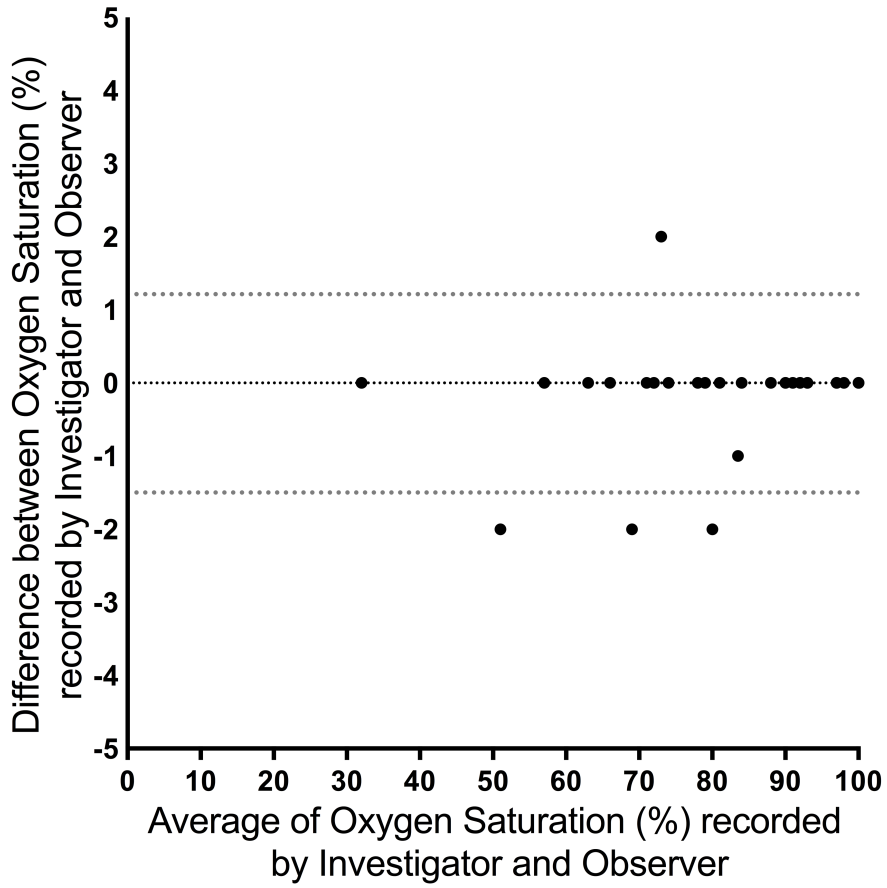
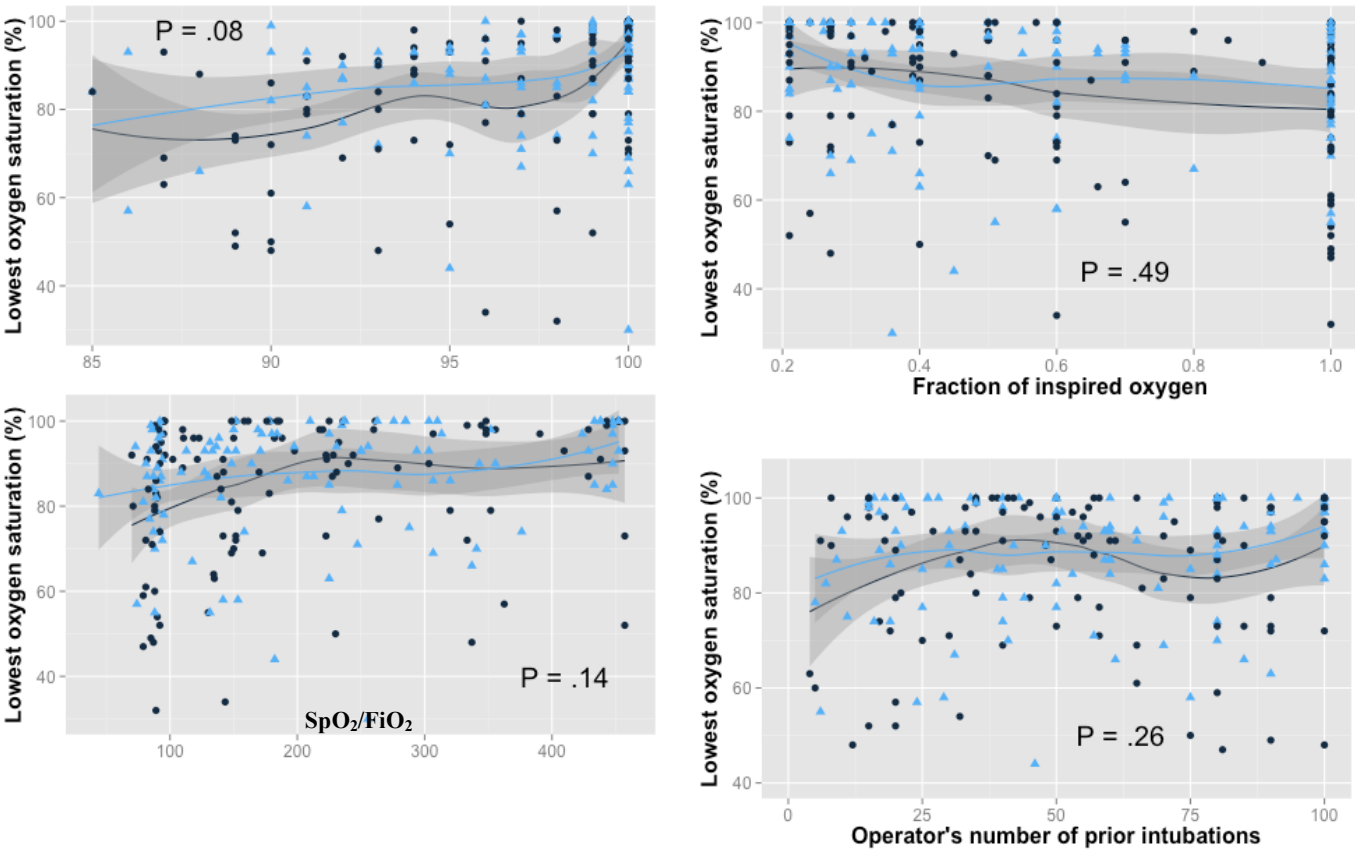
SUPPLEMENTAL FIGURES

e-Figure 1. Bland-Altman plot of lowest arterial oxygen saturation values recorded by the independent observer and the primary investigator.



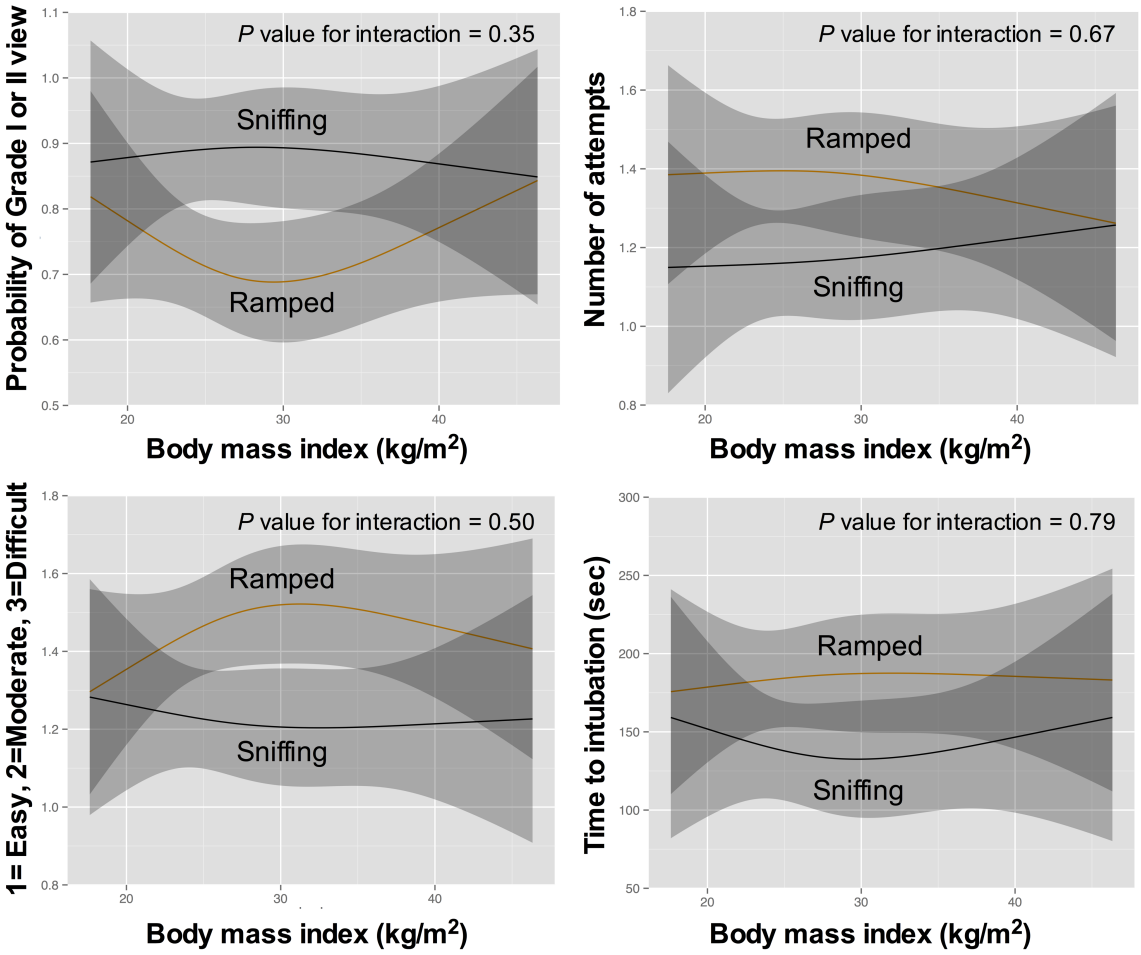
In a convenience sample of 35 (13.5%) study intubations, the primary investigators directly observed the endotracheal intubation procedure and recorded the lowest arterial oxygen saturation separately from the data collection performed by the independent observer. The difference between the value for lowest oxygen saturation recorded by the investigator and the value recorded by the independent observer for each intubation is displayed on the y axis. The average of the lowest oxygen saturation value recorded by the investigator and the value recorded by the independent observer for each intubation is on the x axis. The bias was -0.14 with a standard deviation of 0.69. The 95% limits of agreement were -1.50 to 1.21. There were no instances in which the values for lowest oxygen saturation recorded separately by the primary investigator and the independent observer differed by more than 2%.

e-Figure 2. Lowest oxygen saturation by pre-induction patient and operator characteristics.



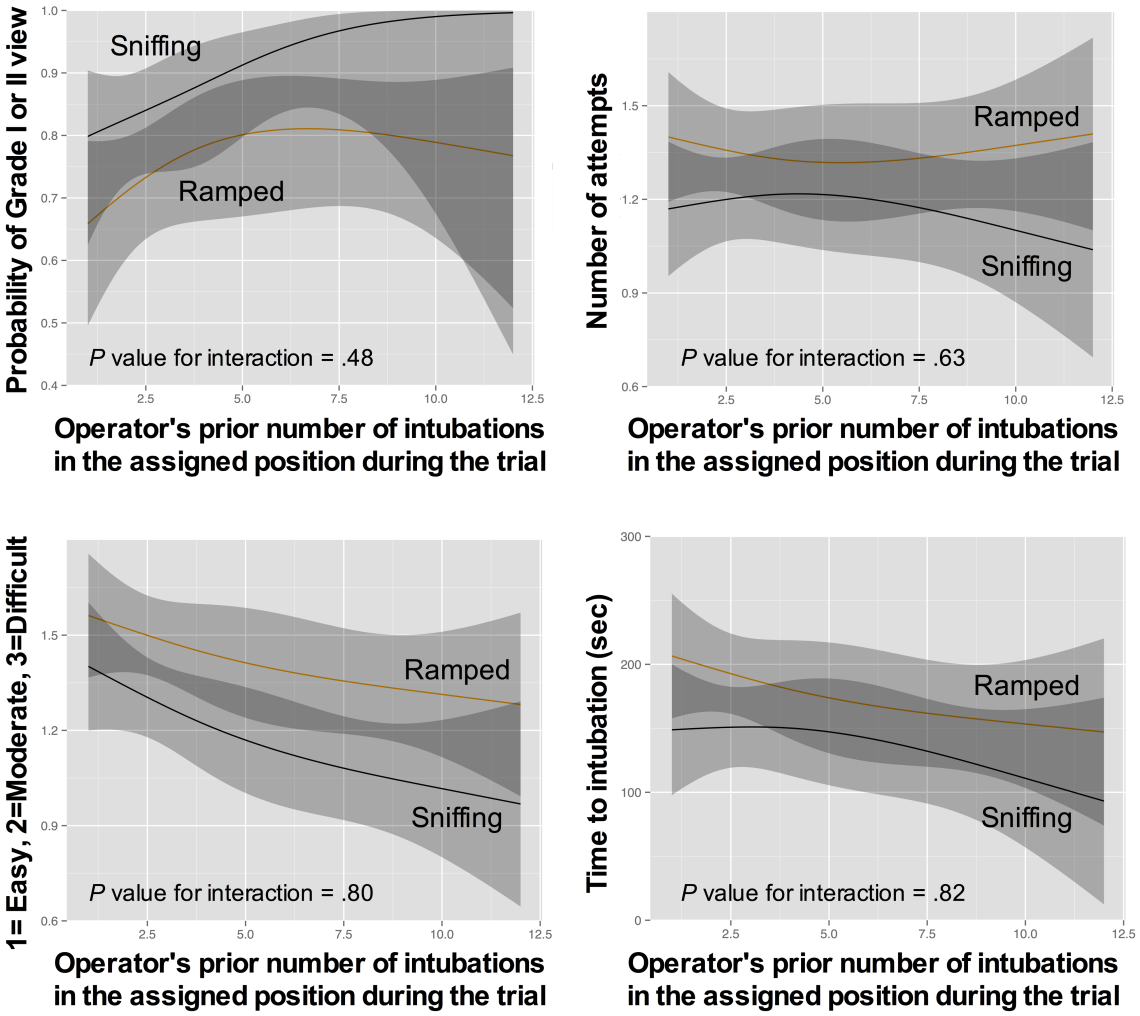
The primary outcome of lowest arterial oxygen saturation is displayed for each patient randomized to ramped position (blue triangles) and sniffing position (black circles). The mean and 95% confidence interval are displayed for each study group across the spectrum of oxygen saturation at induction (upper left), highest fraction of inspired oxygen in the six hours prior to intubation (upper right), lowest ratio of oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2) in the 6 hours prior to intubation (lower left), and the operator's number of prior endotracheal intubations at the time of induction (lower right). *P* values are for the interaction between study group assignment and the variable on the x-axis. SpO_2/FiO_2 ratio is among the 239 patients with an SpO_2 < 97% in the 6 hours prior to intubation.

e-Figure 3. Procedural outcomes relative to body mass index.



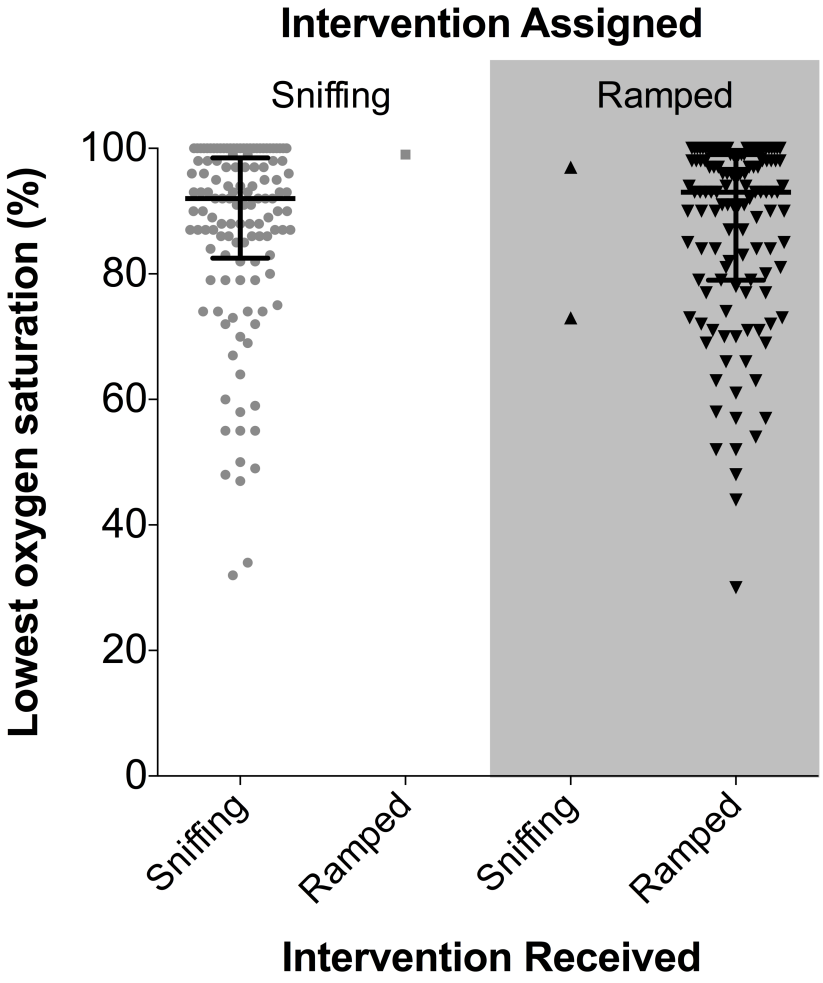
A *post-hoc* exploratory analysis of whether body mass index modified the effect of assigned patient position on Cormack-Lehane grade of view (upper left), number of laryngoscopy attempts required for successful intubation (upper right), operator-assessed difficulty of intubation (lower left), and time from induction to secured airway (lower right). The point estimate and 95% confidence interval are displayed for each group across the spectrum of body mass index. Sniffing position resulted in better grade of view, fewer laryngoscopy attempts, and less difficult intubation than ramped position ($P < .05$ for all). Body mass index did not modify the relationship between patient position and these outcomes (P value for interaction $> .10$ for all).

e-Figure 4. Procedural outcomes relative to operator's prior number of intubations in the assigned patient position.



A *post-hoc* exploratory analysis of whether the operator's prior number of intubations in the assigned position during the trial modified the effect of assigned patient position on Cormack-Lehane grade of view (upper left), number of laryngoscopy attempts required for successful intubation (upper right), operator-assessed difficulty of intubation (lower left), and time from induction to secured airway (lower right). The point estimate and 95% confidence interval are displayed for each group across the spectrum the operator's prior number of intubations in the assigned position during the trial. Sniffing position resulted in better grade of view, fewer laryngoscopy attempts, and less difficult intubation than ramped position ($P < .05$ for all). Operator's prior number of intubations in the assigned position during the trial did not modify the relationship between patient position and these outcomes (P value for interaction $> .10$ for all).

e-Figure 5. Lowest arterial oxygen saturation by intervention assigned and received.



The primary outcome of lowest arterial oxygen saturation between induction and two minutes after completion of endotracheal intubation is displayed by the position assigned and received. Median and interquartile range are displayed.

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e-Appendix 2.

Checklists and Upright Positioning in endotracheal intubation of critically ill patients (Check-UP) Trial

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Study Schema

1.0 Study Summary

Title: Checklists and Upright Positioning in endotracheal intubation of critically ill patients (Check-UP) Trial: A Randomized trial of a pre-procedure checklist and patient positioning to improve the safety of endotracheal intubation of critically ill adults.

Background: Complications are common during endotracheal intubation of critically ill patients. Written checklists and specific patient positioning have been proposed as means of decreasing the rate of procedural complications, but lack efficacy data. We propose a randomized trial to compare use of a written checklist versus no written checklist and ramped versus sniffing position for endotracheal intubation of critically ill adults.

Primary Aims:

- **Positioning:** To compare the effect of ramped versus sniffing position on the lowest arterial oxygen saturation experienced by adults undergoing urgent or emergent endotracheal intubation
- **Checklist:** To compare the effect a written, pre-procedure checklist versus no written checklist on the lowest arterial oxygen saturation and lowest systolic blood pressure during urgent or emergent endotracheal intubation of critically ill adults.

Primary Hypotheses:

- **Positioning:** Ramped positioning will increase the lowest oxygen saturation experienced by adults undergoing urgent or emergent endotracheal intubation
- **Checklist:** A written, pre-procedure checklist completed verbally between an observer and operator will increase the lowest arterial oxygen saturation and lowest systolic blood pressure experienced by adults undergoing urgent or emergent endotracheal intubation.

Inclusion Criteria:

1. Patient is admitted to the Medical Intensive Care Unit (MICU)
2. Planned procedure is endotracheal intubation
3. Planned operator is a Pulmonary and Critical Care Medicine (PCCM) fellow
4. Administration of sedation and/or neuromuscular blockade is planned

Exclusion Criteria:

1. Operator feels specific patient positioning during intubation is required
2. Urgency of intubation precludes safe performance of study procedures, including the time required to complete a pre-procedure checklist

Consent: Given that ramped position, sniffing position, written checklists, and no written checklists are all routinely used approaches to endotracheal intubation by PCCM fellows in the MICU, the lack of established risk or benefit with any of the interventions, and the impracticability of obtaining

informed consent prior to urgent or emergent endotracheal intubation in patients with acute physiologic derangements, a waiver of informed consent will be requested.

Randomization: Using opaque envelopes available in the MICU, participants will be randomized 1:1 to ramped versus sniffing position and checklist versus no checklist.

Study Interventions:

- **Positioning:**
  - **Ramped position** – (1) Head-of-bed raised to 25°, (2) patient's legs and face parallel to ceiling, (3) pillows and/or blankets under patient's head as needed to achieve ear-to-sternal-notch alignment.
  - **Sniffing position** – (1) Entire bed flat, (2) pillows and/or blankets under patient's head and/or shoulders to achieve neck flexion of 35°, (3) head extension of 15°, and (4) ear-to-sternal-notch alignment.

- **Checklist:**
  - Checklist – A non-operator verbally confirms with the operator the completion of preparatory steps listed on a written checklist prior to the administration of procedure-related drugs.
  - No Checklist – No use of a verbally performed, written pre-procedure checklist.

Primary Endpoint:

- **Positioning:**
  - Lowest arterial oxygen saturation

- **Checklist:**
  - Co-primary endpoints
    - Lowest arterial oxygen saturation
    - Lowest systolic blood pressure

Secondary Endpoints for both interventions:

Composite endpoint of life-threatening complications in the hour after intubation (one or more of the following):

- Death within one hour of intubation
- Cardiac arrest within 10 minutes of intubation
- Severe cardiovascular collapse (new SBP < 65 mmHg or new need for vasopressor between medication administration and 2 minutes following successful placement of an endotracheal tube)
- Severe hypoxia (new SpO_2 < 80% between medication administration and 2 minutes following successful placement of an endotracheal tube)

Incidence of desaturation, hypoxemia, change in saturation, grade of view, first pass success, number of attempts, time to intubation, need for additional equipment or operator.

Tertiary Endpoints for both interventions: In-hospital mortality, Ventilator-free days, ICU-free days.

2.0 Background

Endotracheal intubation is common in the care of critically ill patients (1-3). Complications of airway management in this setting are frequently encountered and may be associated with an increased risk of death (1, 2, 4, 5). The prevention of complications during urgent and emergent endotracheal intubation is a key focus for airway management research (4, 6, 7). The use of a written, pre-intubation checklist (4) and positioning the patient with the head of bed elevated (8) have both been proposed as interventions capable of preventing complications during non-elective intubation, but neither have been examined in a prospective trial.

2.1 Complications of Endotracheal Intubation of the Critically Ill

The emergent endotracheal intubation of critically ill patients is associated with an increased risk of complications compared to the intubation of patients in the OR (9). Approximately 30% of emergent endotracheal intubations in the ICU are associated with complications, including: hypoxemia, hypotension, failed intubation, esophageal intubation, airway trauma, aspiration, cardiac arrest, and death (4, 9, 10). In a root cause analysis of complications associated with out-of-OR endotracheal intubation, common variables that contributed to procedural complications included a lack of identification of patients at risk for a difficult airway, incomplete procedural planning, a lack of equipment and supervision by an experienced operator, and a failure to quickly identify and manage procedure-related complications (9, 11).

2.2 Positioning During Endotracheal Intubation

Positioning patients to optimize operator's grade of view and ease of intubation has been a long-standing subject of discussion for elective airway management occurring in the operating room. Anesthesia texts and guidelines frequently recommend intubation with the patient in "sniffing position" in which the body is supine, the neck is flexed forward 30 degrees, and the head is extended backward to produce a 15 degree angle between the plane of the face and the ceiling. Historically, the 'sniffing position' arose from attempts to achieve best laryngeal exposure by placing a pillow under the patient's occiput (12). Multiple anatomic explanations for the advantage of this position have been proposed including the "three axis alignment theory" (13) in which the laryngeal axis, pharyngeal axis, and mouth axis are aligned and the "two curve theory" in which alignment of the oropharyngeal curve and pharyngo-glotto-tracheal curve with the line of site to the trachea promotes laryngeal view (http://lifeinthefastlane.com/ccc/three-axis-alignment-versus-

two-curve-theory/). Despite widespread recommendation and adoption of sniffing position for endotracheal intubation for over 50 years, prospective evaluations of the technique have only recently become available, with conflicting results.

In 2001, Adnet et al evaluated grade of laryngeal view in the sniffing position (achieved with a 7 cm cushion) and supine head extension in 456 patients of all weights undergoing elective surgery. They found that sniffing position improved view in 18% and worsened view in 11%, with obesity and limited neck mobility predicting improvement in view with sniffing. There was no difference in the incidence of difficult intubation as assessed by the operators (11% versus 11%) (14). In 2011, Prakash et al examined grade of laryngeal view with sniffing position compared to supine head extension in 550 adults regardless of weight undergoing elective surgery (15). While they found no difference in grade of view, operators noted lower difficulty of intubation with sniffing position. In 2014, El-Orbany examined grade of laryngeal view with supine head extension, sniffing position at 6 cm of elevation, and supine position at 10 cm of elevation in 167 adults of any weight (16). They found increasing elevation always improved (66%) or maintained (34%) grade of view. Incidence of grade III or IV view was 8% with supine head extension, 2% with sniffing position at 6 cm and 1% with sniffing position at 10 cm.

"Ramped positioning" has been recommended as an alternative to the sniffing position (17) and has been the predominant positioning approach in some patient and operator groups (16). In ramped positioning, the shoulders and head are elevated together toward the point at which the external auditory meatus and sternal notch are aligned. This has been achieved using specialized devices (16), blankets or towels placed under the patient (18), reverse trendelenberg positioning (19), or elevation of just the head of the bed to a pre-specified angle (20). A small number of studies in the operating room have compared ramped position to sniffing position, with regard to grade of laryngeal view. In 2004, Collins et al randomized 60 obese patients undergoing endotracheal intubation to sniffing (7 cm cushion) versus ramped positioning (blankets under shoulders and head until ear-to-sternal notch alignment) and found better grade of view with ramped position (8). In 2007, Lee et al performed a paired study in which the percentage of glottic opening score was compared between supine head extension position and ramped position (head of bed elevated to 25 degrees) in 40 non-obese patients (21). They found improved view with the 25 degree head of bed elevation compared to supine. When ramped position achieved using blankets under the shoulders and head was compared to ramped position achieved by elevating the head of the bed by Rao et al in 2008, no differences were found in in time to intubation or any other variable (18).

While studies of patient positioning during endotracheal intubation have primarily focused on operator grade of view and ease of intubation, intubating position may have the additional potential to impact peri-procedural hypoxemia -- the most common complication of intubation and the complication most closely linked to cardiac arrest and death. Three prior studies have suggested ramped positioning may prevent desaturation. In 2003, Boyce et al randomized 26 obese adults undergoing elective surgery to one of three arms: supine position, reverse trendelenberg, or ramped position achieved by elevating the head of the table to 30 degrees (19). All participants were intubated, ventilated for 5 minutes to a saturation of 100%, disconnected from the ventilator, and monitored for time to desaturation to 92%. The time until desaturation was longer for patients in reverse trendelenberg or ramped position. In 2005, Dixon et al compared supine position and ramped position using head-of-bed elevation in 42 obese adults (20). All patients were placed in the assigned position, pre-oxygenated with 100% FiO2 for 3

minutes, intubated, and then observed without ventilation in the assigned position until arterial oxygen saturation declined to 92%. Duration of apnea without desaturation was significantly longer in those intubated in the ramped position. Similarly, when Lane et al randomized patients to undergo preoxygenation for 3 minutes while supine or with the head of the bed elevated to 20 degrees before undergoing rapid-sequence intubation, the duration of apnea without desaturation was longer for those preoxygenated with the head of the bed elevated (22).

There are currently no studies in patients undergoing non-elective, out-of-operating room intubations comparing the sniffing and ramped positions with regard to procedural factors (grade of operator view) or short-term outcomes (desaturation). Both sniffing and ramped position have been recommended for use in routine care by emergency airway management experts (17) but whether one approach should be considered the optimal choice for routine use in urgent and emergent intubations is unknown. To address this question, a prospective, randomized trial comparing sniffing and ramped position for non-elective intubations is needed.

2.3 Checklists in Critical Care and Endotracheal Intubation

Checklists and protocols have been shown to improve outcomes in the care of the critically ill (23-28). Given the number of factors contributing to procedure-related complications (9) and high acuity environment surrounding urgent intubation, pre-procedure checklists and procedural algorithms are an obvious intervention to prevent complications. Checklist have been developed for intubations occurring in the OR (11, 29) however their utility in critically ill patients with acute physiologic derangements is less clear. In a before-and-after study of a protocol addressing some of the factors listed above contributing to procedural complications, implementation of a intubation protocol in the ICU was associated with a decrease in procedure-related complications (4). Unfortunately, the before-and-after design of the study allows for potential confounding from improvement in operator skill over time and other changes in practice that may have independently influenced outcomes (4), both of which occurred during this study. On the other hand, use of a pre-procedure checklist for the intubation of trauma patients in the emergency department was not associated with any improved procedure-related or outcome variables (30). Others have proposed various procedure checklists to be used without a comparative analysis (29, 31). The conflicting data on the whether outcomes are improved with checklists warrant further study.

Given the conflicting background data and clinical equipoise regarding the use of a written, pre-intubation checklist, the high rate of complications associated with intubation of critically ill patients, and potentially numerous modifiable risk factors, we aim to conduct a randomized trial of a written, pre-procedure checklist to reduce complications compared with no written checklist.

3.0 Rationale, Aims, and Hypotheses

In order to determine the impact of patient position and written checklist use on procedural and clinical outcomes of endotracheal intubation of critically ill patients, a randomized trial is needed.

Study Aims:

- **Primary:**
  - **Positioning:** To compare the effect of ramped versus sniffing position on lowest arterial oxygen saturation in adults undergoing urgent or emergent endotracheal intubation
  - **Checklist:** To compare the effect of using a written, pre-procedure checklist on the lowest arterial oxygen saturation and lowest systolic blood pressure experienced by adults undergoing urgent or emergent endotracheal intubation.
- **Secondary:**
  - To evaluate the effect of the same interventions in the same population on airway management characteristics (first pass success, grade of view, time to completion of intubation, additional devices, additional operators), complications (desaturation, hypotension, esophageal intubation, failed intubation, cardiac arrest, procedural death), and clinical outcomes (ventilator-free days, ICU-free days, and in-hospital mortality).

Study Hypotheses:

- **Primary:**
  - **Positioning:** Ramped positioning will increase lowest oxygen saturation experienced by adults undergoing urgent or emergent endotracheal intubation
  - **Checklist:** A written, pre-procedure checklist verbally performed between a bedside observer and operator will increase lowest arterial oxygen saturation and lowest systolic blood pressure experienced by adults undergoing urgent or emergent endotracheal intubation.

- **Secondary:**
  - **Positioning:** Ramped positioning will improve grade of view, shorten the time to intubation, decrease the need for additional devices and additional operators, decrease complications, and increase ventilator-free days and ICU-free days without impacting in-hospital mortality.
  - **Checklist:** Use of a written, pre-procedure checklist will decrease a composite of life-threatening complications (severe hypoxia, hypotension, cardiac arrest, and death), improve grade of view, shorten the time from induction drug administration to completion of intubation, decrease the need for additional devices and additional operators, decrease complications, and increase ventilator-free days and ICU-free days without impacting in-hospital mortality.

4.0 Study Description

In order to address the aims outlined above, we propose a randomized, parallel-group trial evaluating the impact of (1) ramped versus sniffing position on lowest oxygen saturation and (2) use of a written, pre-procedure checklist versus none on complications during endotracheal intubation in the intensive care unit. Patients admitted to the study ICU who are deemed by their clinical team to require intubation and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to ramped versus sniffing position and checklists use versus none. All other decisions regarding airway management will remain at the discretion of the

treating provider. Data will be collected at the time of intubation and prospectively from the medical record in order to determine the effect of the assigned interventions on short- and long-term outcomes.

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

We will include airway management events in which:

1. Patient is admitted to the Medical Intensive Care Unit (MICU)
2. Planned procedure is endotracheal intubation
3. Planned operator is a Pulmonary and Critical Care Medicine (PCCM) fellow
4. Administration of sedation and/or neuromuscular blockade is planned
5. Age ≥ 18 years old

5.2 Exclusion Criteria:

We will exclude airway management events in which:

1. Operator feels specific patient positioning during intubation is required
2. Urgency of intubation precludes safe performance of study procedures
3. Operator feels an alternative pre-procedure checklist or no checklist is required

6.0 Enrollment/Randomization

6.1 Study Sites: Medical Intensive Care Unit at Vanderbilt University Medical Center

6.2 Study Population: All adults admitted to the MICU at VUMC for whom the clinical team has decided endotracheal intubation using sedation and/or neuromuscular blockade is required and the fellow is the planned first operator. Patients will be excluded only if the intubating fellow or supervising attending feels: 1. a specific patient positioning during the procedure (example: fully upright, ramped, completely supine) is required for the safe performance of the procedure; 2. the urgency of the intubation would make unsafe the time required to open the opaque envelope and perform the needed study procedures; or 3. An alternative pre-procedure checklist or no checklist should be used for the safe performance of the procedure. Patients will be included regardless of gender, race, weight or body mass index, initial oxygen saturation, anticipated grade of view, and other clinical factors.

6.3 Enrollment: All patients will be enrolled at the time the clinical team decides that intubation is required and the patients meets inclusion but not exclusion criteria.

6.4 Consent:

The ramped and sniffing positions have each been promoted as optimal positions in which to intubate acutely ill patients. Both are currently used intermittently in routine practice in the MICU at VUMC. Currently, choice of intubating position is based on provider preference or convenience, as there are no randomized trials or evidence-based guidelines to support the choice of one position over the other for intubations occurring in the MICU.

Airway management experts disagree about the utility of a routine checklist prior to endotracheal intubation in acutely ill patients. In current practice, provider preference and convenience determines to what degree a formal review of the planned procedure occurs prior to its initiation. There are no randomized trials or evidence-based guidelines to support the superiority of a written checklist over no written checklist for intubations occurring in the MICU. Finally, the small amount of available evidence regarding the use of a pre-intubation checklist suggests that it is safe; however the same evidence is conflicting and inconclusive on whether checklists result in improved outcomes. This has resulted in variable use of pre-intubation checklists both inside and outside of the ICU by airway proceduralists.

Because the interventions studied (1) are used as a part of routine care, (2) are interventions the patient would likely be exposed to even if not participating in the study, and (3) are equivalent options from the perspective of the clinical provider (otherwise patient is excluded), we feel the waiver of consent involves no more than minimal risk.

Additionally, obtaining informed consent prior to participation in the study would be impractical. Endotracheal intubation of acutely ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the MICU.

Because the study interventions represent minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

6.5 Randomization:

Computerized randomization using permuted blocks of four or eight will be conducted in order to generate a series of factorialized study assignments deliberately exceeding the planned enrollment number. Study assignments will be placed in opaque randomization envelopes and will be available to PCCM fellows in the MICU. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study. Once it has been determined by the treating team that (1) intubation is required, (2) the PCCM fellow will be the first to attempt the procedure, (3) sedation and/or neuromuscular blockade will be used, (4) a specific patient positioning or checklist use or non-use is not requisite, and (5) urgency of the intubation does not preclude safe performance of study procedures, the operator will open the envelope and follow the factorialized assignment of either ramped versus sniffing position and a written checklist or no written checklist.

7.0 Study Procedures

7.1 Study Interventions

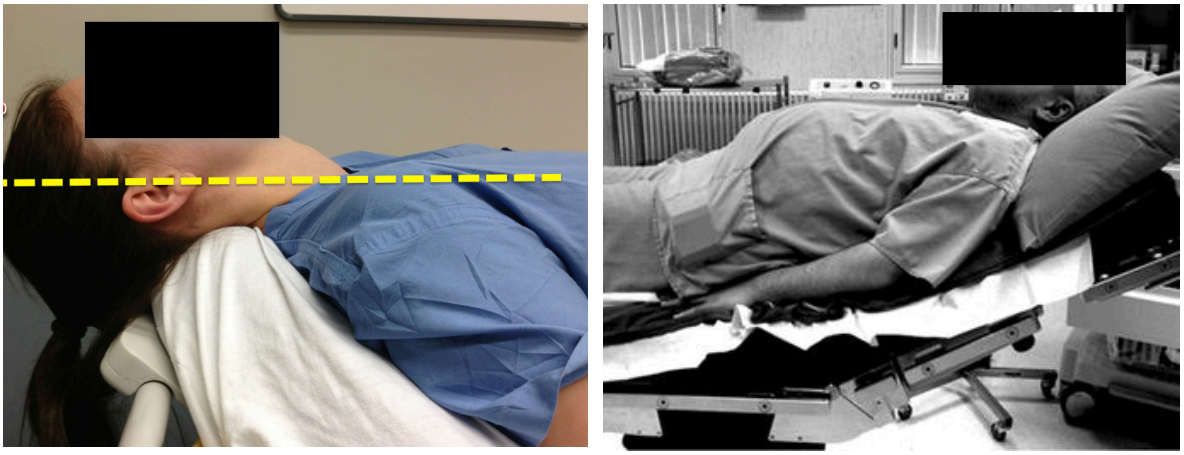
7.1.1 Positioning

Study group assignment will determine the position of the patient at the initiation of laryngoscopy. Once the enveloped is opened and group assignment is known, it is at the discretion of the clinical team when to move the patient into the assigned position, as long as the patient is in the assigned position at the start of laryngoscopy. Although the patient must be in the assigned position at the start of laryngoscopy, if difficulties with airway management are encountered, the provider may revise patient positioning at any time thereafter in order to ensure safe management of the airway – repositioning during the procedure will be prospectively recorded.

Ramped position

The patient will be moved toward the head of the bed until the head and neck are resting on the edge of the mattress. Keeping the lower half of the bed flat, the head of the bed will be raised to an angle of 25°. The patients face will be parallel to the ceiling with neck in slight extension, torso at 25°, and legs parallel to the ceiling. Pillows and/or towels under the head will be added or removed as needed to achieve alignment of the external auditory meatus with the sternal notch. Once desired patient positioning is achieved the entire bed will be moved up or down to place the patient's mouth at a comfortable level for the fellow performing the procedure. Examples of ramped position for airway management procedure are shown in Figure 1.

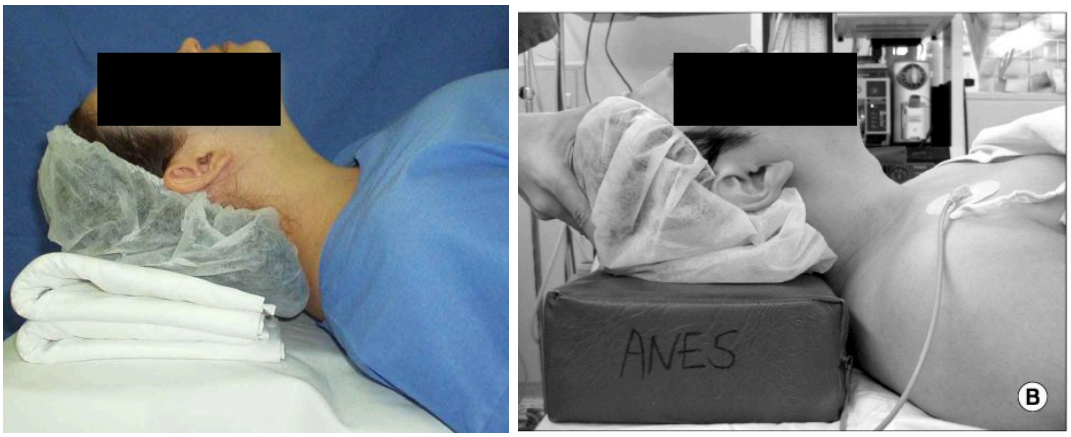
Figure 1. Examples of ramped position.



Sniffing position

With the entire bed flat, pillows and/or blankets will be placed under the patient's head and/or neck. Initially, a goal of 7cm of head elevation will be targeted with the goal of flexion of the neck at 35° relative to the torso and head extension to position the face at a 15° angle to the ceiling. Pillows and/or blankets will be added or removed as needed to achieve alignment of the external auditory meatus and the sternal notch.

Figure 2. Examples of Sniffing Position.



Operator Training

Prior to study initiation, all involved PCCM fellows will be trained in how to position patients in the ramped and sniffing positions. Training will include in-person simulation before the study, an online review of positioning available during the study, and step-by-step instructions available with study materials at the time of the intubation procedure.

Operator Testing

Throughout the course of the study, involved PCCM fellows will undergo random checks of proficiency with ramped and sniffing positioning, the results of which will be recorded.

7.1.2 Checklists

Derivation of the Checklist Intervention and Content Validity

Given the sparse data regarding what components to include in a pre-intubation checklist and equipoise surrounding the efficacy of checklist use, we took a number of steps to ensure that we created a checklist that is based on:

1. Previous checklists used in comparative studies
2. Checklists created by airway experts without comparative analysis

3. A survey of airway experts that we conducted to ensure we included checklist items that are already frequently used

4. Simulation testing of the derived checklist to ensure it would not delay the procedure compared to usual care

5. Observational data obtained from PCCM fellows intubating ICU patients suggesting that the checklist items included were already being performed in usual care but not with a formal, verbally-performed checklist

6. Items that would not be intrusive to the operator performing the procedure (will not mandate use of certain devices, drugs, oxygenation strategies)

As previously mentioned, there are little data regarding the efficacy of pre-intubation checklists and comparative data are limited to sub-optimal before-and-after study designs that are prone to bias and do not allow us to determine causation. In a before-and-after study of a protocol addressing some of the factors listed above contributing to procedural complications, implementation of a intubation protocol in the ICU was associated with a decrease in procedure-related complications (4). Unfortunately, the before-and-after design of the study allows for potential confounders such as operators improving their intubation skills over time and other changes in practice beyond a protocol that may also have influenced outcomes (4), both of which occurred during this study. On the other hand, use of a pre-procedure checklist for the intubation of trauma patients in the emergency department was not associated with any improved procedure-related or outcome variables (30).

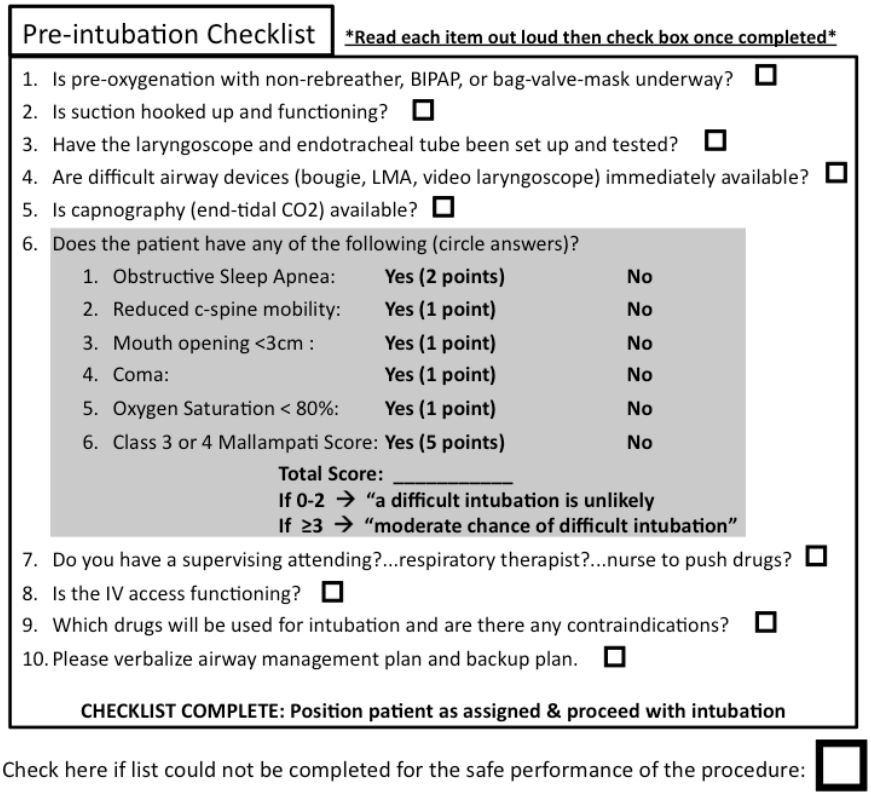
Others have proposed various procedure checklists to be used without a comparative analysis (29, 31); however without studying these checklists as interventions we cannot say that they offer any added benefit to the safe performance of the procedure and patient outcomes. Items from all of the checklists mentioned above were included in our checklist as long as they were pre-procedure steps and did not mandate the use of certain drugs, devices, or positioning.

Given limited efficacy data and a number of pre-intubation checklists already proposed by airway experts for the safe intubation of critically ill patients, we conducted a survey of 21 airway experts from both academic institutions and private practice that included experienced critical care physicians, anesthesiologists, and emergency room physicians. The aim of the survey was to ensure the pre-intubation checklist that we created includes preparatory steps performed frequently in real situations by airway experts and ensure we were not missing any important preparatory steps to increase the content validity of the intervention. All preparatory items included on our checklist were reported by airway experts to be used at least 50% of the time when intubating critically ill patients, the majority of items being used >90% of the time.

Simulation testing of the proposed checklist was performed with PCCM fellows intubating SimMan® patient simulators. Duration from decision to intubate to drugs being pushed and time from drugs to successful intubation were recorded without and then with the use of the pre-procedure checklist. The use of a pre-procedure checklist resulted in similar preparatory and intubation times. Feedback from the participating fellows on the organization of the checklist was incorporated into the current intervention.

Checklist Intervention

The specific intervention that we aim to evaluate is the verbal completion of a written, pre-intubation checklist between the operator and an individual not involved with performance of the procedure compared with no verbally performed writteen checklist. We do not aim to evaluate individual checklist items or compare our checklist to other checklists previously published. After the above derivation process to create the checklist, we developed the checklist intervention to be used in the trial (**Figure 3**). At the time where the critical care team has decided that a patient requires endotracheal intubation, the PCCM fellow is the planned first operator, and they have determined that the patient does not require a certain HOB positioning strategy or alternative checklist for the safe performance of the procedure, patients will be randomized to either the use of a pre-procedure checklist or no checklist. When randomized to a pre-procedure checklist, the independent observer will read aloud each item to the operator prior to the administration of intubation medications. Once the operator verbally confirms that each checklist item has been performed, the independent observer will place a mark next to that checklist item. Although the checklist is designed to be quickly performed and only includes items that airway experts would have likely done even without a checklist, at any time for the safety of the patient, the operator, critical care attending, or anyone else participating in the procedure can interrupt the performance of the checklist and proceed directly to intubation. Patients will be analyzed by intention-to-treat regardless of whether the checklist was completed prior to the administration of procedure-related medications. The number of incomplete checklist items will be recorded for patients randomized to the checklist group.



Pre-intubation Checklist *Read each item out loud then check box once completed*

1. Is pre-oxygenation with non-rebreather, BIPAP, or bag-valve-mask underway? ☐
2. Is suction hooked up and functioning? ☐
3. Have the laryngoscope and endotracheal tube been set up and tested? ☐
4. Are difficult airway devices (bougie, LMA, video laryngoscope) immediately available? ☐
5. Is capnography (end-tidal CO2) available? ☐
6. Does the patient have any of the following (circle answers)?

1.	Obstructive Sleep Apnea:	Yes (2 points)	No
2.	Reduced c-spine mobility:	Yes (1 point)	No
3.	Mouth opening <3cm :	Yes (1 point)	No
4.	Coma:	Yes (1 point)	No
5.	Oxygen Saturation < 80%:	Yes (1 point)	No
6.	Class 3 or 4 Mallampati Score:	Yes (5 points)	No

Total Score: _____
If 0-2 → "a difficult intubation is unlikely
If ≥3 → "moderate chance of difficult intubation"

7. Do you have a supervising attending?...respiratory therapist?...nurse to push drugs? ☐
8. Is the IV access functioning? ☐
9. Which drugs will be used for intubation and are there any contraindications? ☐
10. Please verbalize airway management plan and backup plan. ☐

CHECKLIST COMPLETE: Position patient as assigned & proceed with intubation

Check here if list could not be completed for the safe performance of the procedure: ☐

Figure 3. The checklist Intervention to be read aloud by the independent observer and each item marked when confirmed by the operator

8.2 Data Collection

Baseline: Age, gender, height, weight, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, mean arterial pressure and vasopressor use prior to intubation, noninvasive ventilator

use, highest FiO_2 delivered in prior 6 hours, lowest oxygen saturation in prior six hours, pH, PaO_2, $PaCO_2$, indication for intubation, reintubation, preoxygenation technique, operator experience, additional personnel available

Peri-procedural: Date and time of sedative and/or neuromuscular blocker administration, saturation at time of sedative and/or neuromuscular blocker administration, sedative, neuromuscular blocker, ventilation between induction and laryngoscopy, tube characteristics, route, laryngoscope type and size, total number of attempts, tube tape level, confirmation of placement technique, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications (esophageal intubation, aspiration, airway trauma), arrhythmia requiring therapy, patient positioning, re-positioning during the procedure, number of checklist items completed in patients assigned to checklist. Lowest arterial oxygen saturation, lowest systolic blood pressure, vasopressor administration, time to intubation and other key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure.

0-6 hours: Post-intubation imaging, post intubation shock or cardiac arrest, SaO_2, FiO_2, PEEP, and MAP at 1 and 6 hours after intubation

In-Hospital Outcomes: Date of extubation (ventilator-free days), date of ICU discharge (ICU-free days), date of death

8.3 Outcome Measures

Primary Endpoint:

- **Positioning:**
  - "Lowest arterial oxygen saturation" defined as lowest non-invasively measured arterial oxygen saturation between the time of induction or neuromuscular blockade and two minutes after completion of the airway management procedure.
- **Checklist:**
  - Co-primary endpoints:
    - Lowest arterial oxygen saturation (as above)
    - "Lowest systolic blood pressure" defined as the lowest non-invasively or invasively measured systolic blood pressure between medication administration and 2 minutes following successful placement of an endotracheal tube.

Secondary and Tertiary Endpoints:

Positioning:

Secondary Outcomes

1. Incidence of desaturation as defined by a decrease in oxygen saturation of greater than 3% from induction to lowest oxygen saturation (ex: 96% to 92%)
2. Incidence of hypoxemia as defined by lowest oxygen saturation less than 90% and severe hypoxemia as defined by lowest oxygen saturation less than 80%
3. Change in saturation from induction to lowest oxygen saturation
4. Lowest oxygen saturation adjusting for oxygen saturation at induction
5. Cormack-Lehane grade of view on first attempt
6. Incidence of "first pass success" defined as "placement of an endotracheal tube in the trachea after the first insertion of the laryngoscope into the oral cavity without the use of any other devices"
7. Number of attempts required for successful tube placement
8. Time to intubation
9. Incidence of need for additional intubating equipment, second operator
10. Incidence of non-oxygenation complications – composite of all other recorded complications
11. Incidence of post-intubation tube malposition on CXR
12. Incidence of repositioning after procedure initiation

Tertiary outcomes

1. In-hospital mortality
2. Ventilator-free days (VFDs)
3. ICU-free days (ICUFDs)

Checklist:

Secondary Outcomes

1. Composite endpoint of life-threatening complications after intubation (one or more of the following):
    i. Death within one hour of intubation
    ii. Cardiac arrest within 10 minutes of intubation
    iii. Severe cardiovascular collapse (new SBP < 65 mmHg or new need for vasopressor between medication administration and 2 minutes following successful placement of an endotracheal tube)
    iv. Severe hypoxia (new SpO_2 < 80% between medication administration and 2 minutes following successful placement of an endotracheal tube)
2. The incidence of each component of the composite endpoint (death, cardiac arrest within 10 minutes of procedure completion, severe hypoxia, cardiovascular collapse)
3. Time from starting the checklist to successful endotracheal intubation
4. Time from administering induction medications to successful endotracheal intubation
5. Number of checklist items completed
6. Incidence of checklist interruption to proceed with the procedure
7. Incidence of desaturation as defined by a decrease in oxygen saturation of greater than 3% from induction to lowest oxygen saturation (ex: 96% to 92%)
8. Incidence of hypoxia as defined by lowest oxygen saturation less than 90%
9. Change in saturation from induction to lowest oxygen saturation

10. Lowest oxygen saturation adjusting for oxygen saturation at induction
11. Cormack-Lehane grade of view on first attempt
12. Incidence of "first pass success" defined as "placement of an endotracheal tube in the trachea after the first insertion of the laryngoscope into the oral cavity without the use of any other devices"
13. Number of attempts required for successful tube placement
14. Incidence of need for additional intubating equipment, second operator
15. Incidence of non-oxygenation complications – composite of all other recorded complications
16. Incidence of post-intubation tube malposition on CXR
17. Incidence of repositioning after procedure initiation

Tertiary outcomes

1. In-hospital mortality
2. Ventilator-free days (VFDs)
3. ICU-free days (ICUFDs)

ICU-free days to 28 days after enrollment will be defined as the number of midnights alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit before 28 days. If the patient is admitted to an intensive care unit service at day 28 or dies prior to day 28, ICU-free days will be 0.

Ventilator-free days to day 28 will be defined as the number of midnights alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0.

8.0 Risks and Benefits:

In patients for whom the treating team has decided endotracheal intubation is required, there are currently no established risks or benefits to intubation in the ramped versus sniffing position or with or without a written checklist. Additionally, in our survey of a variety of airway experts, all items included in the checklist intervention would have been performed in usual care even without the use of a written checklist. We expect that checklist items will occur in both groups and the intervention that patients will be exposed to is only a verbalized version of these items. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients requiring endotracheal intubation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective airway management for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

This study will take place in the environment of the intensive care unit at the time of a procedure required for routine clinical care. Thus, at the time of the study intervention, the patient will have in the room a PCCM or anesthesia attending, a PCCM fellow, an ICU nurse, and usually a respiratory therapist in addition to continuous invasive or non-invasive monitoring. Additionally, study personnel will readily available to answer questions at any time during the study course. Even after randomization if any healthcare provider participating in the intubation procedure believes that the study interventions cannot be performed for the safe performance of the procedure, the study intervention is halted and the patient is intubated in the manner which the clinical team judges to be safest.

9.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) is defined as any unexpected and untoward medical occurrence that meets any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be

monitoring the patients continuously for adverse events and serious adverse events. Serious and unexpected adverse events associated with study interventions will be recorded in a case report form in the study record and reported to the IRB within 10 business days. As endotracheal intubation in the critical care setting is known to be independently associated with numerous adverse events including failed attempts at intubation, esophageal intubation, arterial oxygen desaturation, aspiration, hypotension, cardiac arrest, and death, these events will be continuously monitored by study personnel to determine if a preponderance of adverse events in one study group merits stoppage of the trial. However, in the absence of an imbalance of the above events between study groups, these events are expected in the routine performance of the airway management procedure and will not be individually recorded and reported to the IRB as unexpected adverse events.

As an additional safety measure, the exclusion criteria specifically state that airway management events in which the operator foresees the potential need for specific positioning or urgency precluding performance of study procedures will not be included in the trial so all airway management events studied will be those in which the treating clinical felt equipoise between the interventions being examined. Further, only the conditions at initiation of the airway management event are proscribed by the study protocol and if at any time during the procedure the operator chooses to employ an alternative airway management strategy they are free to do so.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

Sample Size Determination:

INITIAL SAMPLE SIZE CALCULATION (6/24/15):

"As previous studies have shown that the standard deviation of the lowest oxygen saturation is 10% and a clinically meaningful difference between groups would be 5%, we will have to randomize a total of 170 airway events to give us 90% power at an alpha level of 0.05 to detect

this difference. Additionally, randomization of 170 airway events will give us 86% power to detect a difference in systolic blood pressure of 10 mmHg between groups (4)."

REVISED SAMPLE SIZE CALCULATION (3/24/16):

Our initial sample size calculation utilized an anticipated standard deviation in lowest arterial oxygen saturation of 10% based on previous studies in critically ill adults. How accurately this estimate would represent the observed standard deviation in our study population carried considerable uncertainty. Therefore, after six months of enrollment in the current CHECK-UP trial, we evaluated the standard deviation for the lowest arterial oxygen saturation for all patients enrolled, with group assignments concealed. The observed standard deviation in the first six months of the current trial was 14%, significantly higher than the predicted 10%. In order to preserve adequate power we re-calculated a larger sample size. Using the observed standard deviation of 14% and a clinically meaningful difference in lowest arterial oxygen saturation between groups of 5%, maintaining 80% statistical power at an alpha level of 0.05 would require a total of 248 patients. Anticipating a low rate of missing data for the primary outcome, we selected a final sample size of 260 total patients.

Of note, among all patients enrolled in the first six months of the current CHECK-UP trial, the standard deviation in lowest systolic blood pressure was 30 mmHg. Randomization of 260 airway events will provide 76.4% power to detect a 10 mmHg difference in systolic blood pressure between groups with an alpha of 0.05.

Statistical Analysis:

Analysis principles

- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All hypothesis tests will be two sided, with an α of 0.05 unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Subgroup analyses will be performed irrespective of treatment efficacy.

Trial profile:

We will present a Consolidated Standards of Reporting Trials diagram as Figure 1 to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:

To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile

ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for intubation; Active illnesses at the time of intubation; Severity of Illness (APACHE II score); Respiratory status pre-intubation; Airway management procedure (Preoxygenation technique, Saturation at

time of induction, Induction medication, Neuromuscular blocker, Laryngoscope

type).

Primary Analyses:

*Unadjusted test of treatment effect**.***

Positioning: We will test the hypothesis that ramped position is superior to sniffing position by comparing the lowest arterial oxygen saturation from induction until two minutes after placement of an intra-tracheal airway in patients randomized to the ramped position versus sniffing position groups. The primary outcome lowest oxygen saturation will be treated as a continuous variable and the difference between the two groups will be compared using the Mann-Whitney U test. All other comparisons will be considered secondary analyses.

Checklist: The primary endpoint in the checklist analysis will be a co-primary endpoint of lowest oxygen saturation and lowest systolic blood pressure and both will be treated as a continuous variables. The differences between the two groups will be compared using the Mann-Whitney U test. All other comparisons will be considered secondary analyses.

Secondary Analyses:

Per-Protocol Analysis of Primary Outcomes.

Positioning:

We will test the hypothesis that receipt of ramped position is associated higher lowest oxygen saturation than receipt of sniffing position in a pre-specified per-protocol analysis comparing lowest oxygen saturation as a continuous variable using the Mann-Whitney U test between patients who received ramped position and those that received sniffing position, regardless of randomized study group assignment.

Checklist: In addition to the intention-to-treat analysis, we will conduct a per protocol analysis of the primary outcome comparing patients with completed checklists to patients with incomplete checklists and to patients randomized to no checklist.

Analysis of Secondary and Tertiary Outcomes.

We will conduct unadjusted analysis examining the treatment effect of ramped positioning versus sniffing position and written checklist versus no written checklist on each of the pre-specified secondary and tertiary outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the Fischer exact test.

Subgroup Analyses.

We will conduct unadjusted analysis examining the treatment effect of ramped positioning versus sniffing position on lowest oxygen saturation and written checklist versus no written checklist on life-threatening complications in each of the pre-specified subgroups. Data will be presented as odds ratios and 95% confidence intervals for categorical variables and as mean differences and 95% confidence intervals for continuous variables.

Modeling to Examine Potential Interactions

We will test for heterogeny of treatment effect across each of the prespecified subgroups using multivariable regression with the primary outcome as the dependent variable, study group and the subgroup of interest as independent variables along with relevant confounders, and a cross-product interaction term. Subgroup variables which are continuous will not be artificially dichotomized. Significance will be determined by p value for the interaction term. We will specifically test for an intervention between the factorialized interventions.

Modeling to Examine Potential Confounding Factors.

We will develop a multiple regression model with the primary outcome as the dependent variable and study group and relevant confounders included as independent variables.

Presentation of Statistics

Continuous variables will be described as mean and standard deviation or median and 25th percentile – 75th percentile or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as percentage and number. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests and Fisher's exact test for categorical variables. Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking.

Data collected from the medical record will be entered into the secure online database Redcap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data is verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database Redcap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed after enrollment for 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database Redcap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data is verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database Redcap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

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e-Appendix 3.

Checklists and Upright Positioning in endotracheal intubation of critically ill patients (Check-UP) Trial

Data Analysis Plan:

Ramped Position vs Sniffing Position

Background

Critically ill patients frequently require endotracheal intubation[1]. Hypoxemia is the most common complication of endotracheal intubation outside of the operating room, and the complication most closely linked to cardiac arrest and death[2]. Specific patient positions have been hypothesized to reduce the risks of hypoxemia during endotracheal intubation[3], however, whether patient position during emergent endotracheal intubation affects the incidence of hypoxemia is currently unknown.

Anesthesia texts and guidelines frequently recommend intubation with the patient in "sniffing position" in which the body is supine, the neck is flexed forward 30 degrees, and the head is extended backward to produce a 15 degree angle between the plane of the face and the ceiling. The "ramped position" has been recommended as an alternative to the sniffing position[4] and has been the predominant positioning approach in some patient and operator groups[5]. In the ramped position, the shoulders and head are elevated together toward the point at which the external auditory meatus and sternal notch are aligned. This has been achieved using specialized devices[5], blankets or towels placed under the patient[6], reverse trendelenberg positioning[7], or elevation of just the head of the bed to a pre-specified angle[8].

Studies in the operating room have found improved grade of view and glottic opening with ramped compared to sniffing position[9,10]. Ramped position has also been suggested to improve pre-oxygenation and prevent desaturation during endotracheal intubation by increasing functional residual capacity[7,8,11]. Only a single observational study has compared sniffing and ramped position for intubation outside of the operating room and found fewer complications with the ramped position[3].

Given the paucity of data to guide choice of patient position during endotracheal intubation outside of the operating room, we aim to conduct a randomized trial comparing ramped to sniffing position during endotracheal intubation of critically ill adults.

NOTE: In addition to comparing ramped with sniffing position, the CHECK-UP will be factorialized to compare use of a written, pre-intubation checklist with no written checklist with regard to complications of endotracheal intubation. Details of that design and analysis will be available separately.

Design: The CHECK-UP Trial will be a prospective, parallel-group, open-label, multicenter, randomized trial comparing ramped versus sniffing position with regard to the lowest arterial oxygen saturation during endotracheal intubation of critically ill adults.

Study Hypotheses: Ramped positioning during endotracheal intubation will result in a higher lowest arterial oxygen saturation compared with sniffing position.

Study Sites: The medical intensive care units of Vanderbilt University Medical Center, University Medical Center New Orleans, Ochsner Medical Center, and University of Alabama at Birmingham.

Study Population: Adults undergoing intubation in the medical intensive care unit.

Inclusion Criteria:

1. Patient is located in a participating intensive care unit
2. Planned procedure is endotracheal intubation
3. Planned operator is a Pulmonary and Critical Care Medicine (PCCM) fellow
4. Administration of sedation and/or neuromuscular blockade is planned
5. Age ≥ 18 years old

Exclusion Criteria:

1. Operator feels specific patient positioning during intubation is required
2. Urgency of intubation precludes safe performance of study procedures
3. Operator feels an alternative pre-procedure checklist or no checklist is required

Enrollment: All patients will be enrolled at the time the clinical team decides that intubation is required and the patients meets inclusion but not exclusion criteria.

Consent: Because the ramped and sniffing positions (1) are both used as a part of routine care, (2) are interventions the patient would likely be exposed to even if not participating in the study, and (3) are equivalent options from the perspective of the clinical provider (otherwise patient is excluded) AND obtaining informed consent prior to participation in the study would be impracticable, each of the institutional review boards approved the study with waiver of informed consent.

Randomization: Computerized randomization using permuted blocks of four, eight, or twelve will be used to generate a series of factorialized study assignments deliberately exceeding the planned enrollment number. Randomization will be stratified by study site. Study assignments will be placed in opaque randomization envelopes and will be available to PCCM fellows in participating

ICUs. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study.

Blinding: Given the nature of the study intervention, patients, clinicians, and investigators will not be blinded to group assignment.

Study Interventions: Study group assignment will determine the position of the patient at the initiation of laryngoscopy, but will not affect any other aspect of the procedure.

Ramped position: Patients assigned to ramped position will be moved toward the head of the bed until the head and neck are resting on the edge of the mattress. Keeping the lower half of the bed flat, the head of the bed will be raised to an angle of 25°. Pillows and/or towels under the head will be added or removed as needed to achieve alignment of the external auditory meatus with the sternal notch.

Sniffing position: With the entire bed flat, pillows and/or blankets will be placed under the patient's head and/or neck. Initially, a goal of 7cm of head elevation will be targeted with the goal of flexion of the neck at 35° relative to the torso and head extension to position the face at a 15° angle to the ceiling. Pillows and/or blankets will be added or removed as needed to achieve alignment of the external auditory meatus and the sternal notch. The patients' shoulders will NOT be elevated.

Data Collection

Baseline: Age, gender, height, weight, race, APACHE II score, chronic comorbidities, active medical problems at the time of intubation, active comorbidities complicating intubation, indication for intubation mean, arterial pressure and vasopressor use prior to intubation, noninvasive ventilation use, highest FiO_2 delivered in prior 6 hours, lowest oxygen saturation in prior 6 hours, reintubation, preoxygenation technique, operator experience.

Peri-procedural: Date and time of sedative and/or neuromuscular blocker administration, saturation at time of sedative and/or neuromuscular blocker administration, sedative, neuromuscular blocker, ventilation between induction and laryngoscopy, tube characteristics, route, laryngoscope type and size, total number of attempts, tube tape level, confirmation of placement technique, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications, patient positioning, and re-positioning during the procedure. Lowest arterial oxygen saturation, lowest systolic blood pressure, vasopressor administration, time to intubation and other key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure. To confirm the accuracy of data

collected by the independent observers, the primary investigators will concurrently assess the same outcomes for a convenience sample of around 10% of study intubations.

0-6 hours: Post-intubation imaging, post intubation shock or cardiac arrest, SaO_2, FiO_2, PEEP, and MAP at 1 and 6 hours after intubation

In-Hospital: Date of extubation (ventilator-free days), date of ICU discharge (ICU-free days), date of death

Outcomes

Primary Outcome: The lowest arterial oxygen saturation measured by continuous pulse oximetry (SpO2) between induction and 2 minutes after completion of the airway management procedure ("lowest arterial oxygen saturation").

Secondary Outcomes:

Oxygenation Outcomes:

1. Incidence of lowest oxygen saturation less than 90%
2. Incidence of lowest oxygen saturation less than 80%
3. Change in saturation from induction to lowest oxygen saturation
4. Incidence of desaturation as defined by a decrease in oxygen saturation of greater than 3% from induction to lowest oxygen saturation

Procedural Outcomes:

5. Incidence of patient repositioning after procedure initiation
6. Lowest systolic blood pressure between medication administration and two minutes after completion of the airway management procedure
7. New systolic blood pressure < 65 mmHg or new need for vasopressor between medication administration and 2 minutes following successful placement of an endotracheal tube
8. Cardiac arrest within 10 minutes of intubation
9. Death within one hour of intubation
10. Aspiration, esophageal intubation, airway trauma
11. Cormack-Lehane grade of glottic view
12. Operator-assessed difficulty of intubation
13. Intubation on the first laryngoscopy attempt
14. Number of laryngoscopy attempts
15. Time from induction to intubation
16. Need for additional airway equipment or a second operator
17. Incidence of post-intubation tube malposition on chest x-ray

Tertiary outcomes:

1. In-hospital mortality
2. Ventilator-free days (VFDs)
3. ICU-free days (ICUFDs)

ICU-free days to 28 days after enrollment will be defined as the number of midnights alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit before 28 days. If the patient is admitted to an intensive care unit service at day 28 or dies prior to day 28, ICU-free days will be 0.

Ventilator-free days (VFD) to day 28 will be defined as the number of midnights alive and with unassisted breathing to day 28 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0.

Sample Size Determination:

INITIAL SAMPLE SIZE CALCULATION (6/24/15):

"As previous studies have shown that the standard deviation of the lowest oxygen saturation is 10% and a clinically meaningful difference between groups would be 5%, we will have to randomize a total of 170 airway events to give us 90% power at an alpha level of 0.05 to detect this difference. Additionally, randomization of 170 airway events will give us 86% power to detect a difference in systolic blood pressure of 10 mmHg between groups."

REVISED SAMPLE SIZE CALCULATION (3/24/16):

Our initial sample size calculation utilized an anticipated standard deviation in lowest arterial oxygen saturation of 10% based on previous studies in critically ill adults. How accurately this estimate would represent the observed standard deviation in our study population carried considerable uncertainty. Therefore, after six months of enrollment in the current CHECK-UP trial, we evaluated the standard deviation for the lowest arterial oxygen saturation for all patients enrolled, with group assignments concealed. The observed standard deviation in the first six months of the current trial was 14%, significantly higher than the predicted 10%. In order to preserve adequate power we re-calculated a larger sample size. Using the observed standard deviation of 14% and a clinically meaningful difference in lowest arterial oxygen saturation between groups of 5%, maintaining 80% statistical power at an alpha level of 0.05 would require a

total of 248 patients. Anticipating a low rate of missing data for the primary outcome, we selected a final sample size of 260 total patients.

Statistical Analysis:

Analysis principles

- Primary analysis will be conducted on an intention-to-treat basis (patients with protocol violations are analyzed per the assigned treatment arm).
- All tests will be two-sided with an α of 0.05 defined as significance unless otherwise specified.
- All analyses will be unadjusted unless otherwise specified.
- Analyses for heterogeny of treatment effect (subgroups) will be performed irrespective of treatment efficacy.

Trial profile: We will present a Consolidated Standards of Reporting Trials diagram as Figure 1 to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics: To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with standard deviations or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI, co-morbidities); Indication for intubation; Active illnesses at the time of intubation; Severity of Illness (APACHE II score); Respiratory status pre-intubation; Airway management procedure (Preoxygenation technique, Saturation at time of induction, Induction medication, Neuromuscular blocker, Laryngoscope type); Operator prior experience.

Primary Analysis:

*Unadjusted test of treatment effect**.*** We will test the hypothesis that ramped position is superior to sniffing position by comparing the lowest arterial oxygen saturation in patients randomized to the ramped position versus sniffing position groups. The primary outcome of lowest arterial oxygen saturation will be treated as a continuous variable and the difference between the two groups will be compared using the Mann-Whitney U test. All other comparisons will be considered secondary analyses.

[Of note, pre-oxygenation in ramped vs sniffing position may result a difference between groups in oxygen saturation at the time of induction. A difference in oxygenation at the time of induction might affect the lowest arterial oxygen saturation during the procedure. In the unadjusted primary analysis, any effect of the assigned position on the primary outcome will be considered an effect of the position on the outcome, even if it occurs via impact of pre-induction

positioning on adequacy of pre-oxygenation. In a secondary analyses detailed below, we will adjust for the oxygen saturation at the time of induction to determine whether patient position after induction affects the lowest oxygen saturation during the procedure independently of any effect on pre-oxygenation].

Pre-specified Secondary Analyses:

Analysis of Secondary and Tertiary Outcomes: We will conduct unadjusted analysis examining the treatment effect of ramped positioning versus sniffing position on each of the pre-specified secondary and tertiary outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the Fischer exact test.

Heterogeny of Treatment Effect ('subgroup', 'effect modification', or 'interaction' analyses): We will assess whether the direction or magnitude of the treatment effect differs based on a pre-specified set of variables (1) available at baseline or (2) arising during the procedure. We will fit a linear regression model for the outcome of lowest arterial oxygen saturation; independent variables will include study group assignment, the potential modifier variable of interest, and the interaction between the two (e.g., study_group*BMI). Significance will be determined by the *P* value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analyzed as continuous variables in the model and preferentially displayed as continuous variables. If space available for presentation of results requires dichotomization of continuous variables for inclusion in the forest plot, the value at which the continuous variables will be dichotomized as pre-specified in brackets below. We pre-specify a total of 13 modifier variables ('subgroups'), of which two are of special mechanistic interest (body mass index and Lowest SpO_2 to FiO_2 ratio in the 6 hours prior to intubation) and the remaining 11 are considered confirmatory. With 13 'subgroup' analyses at an α of 0.05, there is around a 50% chance of one or more false-positive results, and the subgroup analyses will be interpreted with this in mind.

Variables available at procedure initiation

1. **Body mass index (kg/m^2) [30 kg/m^2]**
2. Laryngoscope [Video/Direct]
3. Oxygen saturation at the time of induction [95%]
4. Highest FiO_2 in the 6 hours prior to intubation [0.50]
5. Lowest SpO_2 in the 6 hours prior to intubation [90%]
6. **Lowest SpO_2 to FiO_2 ratio in the 6 hours prior to intubation [200]**
7. Noninvasive ventilation receipt in the 6 hours prior to intubation [y/n]
8. Operator's prior airway management experience [50 prior intubations]
9. MACOCHA Intubation Score (*among patients assigned to checklist in the factorial design*) [3]

Variables arising during the procedure

1. Number of intubation attempts [one/multiple]
2. Airway difficulty [easy/moderate or difficult]
3. Time from induction to successful intubation [120 seconds]
4. Receipt of ventilation between induction and laryngoscopy [y/n]

We will also test for an interaction between factorialized patient positioning and checklist intervention group assignments.

Multivariable Modeling: We will develop three multivariable linear regression models for the outcome of lowest arterial oxygen saturation. Model 1 – independent variables will include study group assignment and oxygen saturation at induction. Model 2 – independent variables will include study group assignment, oxygen saturation at induction, age, body mass index, APACHE II score, highest FiO_2 in the 6 hours prior, use of a video laryngoscope, and operator prior intubating experience. Model 3 – independent variables will include study group assignment, oxygen saturation at induction, age, body mass index, APACHE II score, highest FiO_2 in the 6 hours prior, use of a video laryngoscope, operator prior intubating experience, and study_group*body_mass_index (as a cross-product interaction term).

Per-Protocol Analysis of Primary Outcomes: We will test the hypothesis that receipt of ramped position is associated with higher lowest oxygen saturation than receipt of sniffing position in a pre-specified per-protocol analysis comparing lowest oxygen saturation as a continuous variable using the Mann-Whitney U test between patients who received ramped position and those that received sniffing position, regardless of randomized study group assignment.

***Post hoc* Secondary Analyses:** In the event that the investigators, reviewers, or journal editors feel an additional analysis is needed beyond those specified here, the analysis will be clearly identified as '*post hoc'* and will be considered hypothesis generating.

Missing Data:

The primary outcome of lowest oxygen saturation relies on the availability of non-invasive pulse oximeter measurement throughout the intubation procedure. We anticipate that in a small number of cases measurement of lowest oxygen saturation will not be feasible (e.g., due to poor plethysmographic waveform in a hypotensive patient). Our sample size calculation enrolls additional patients to account for around a 5% rate of missing data for the primary outcome.

In the initial analysis, cases with data missing for the primary endpoint will not be included. As sensitivity analyses, the primary analysis will be repeated with missing data imputed by (1) "carrying forward" the saturation at the time of induction (when available) to the lowest oxygen saturation values, (2) assigning a value of 100% to data missing from the ramped group and a value of 0% to data missing from the sniffing group (least conservative), and (3) assigning a value of 0% to data missing from the ramped group and a value of 100% to data missing from the sniffing group (most conservative).

Presentation of Statistics: Continuous variables will be described as mean and standard deviation, median and 25th percentile – 75th percentile, or median and bootstrapped 95% confidence intervals, as appropriate. Categorical variables will be given as frequency and percentage (or percentage and bootstrapped 95% confidence interval, as appropriate). Between-group comparisons for continuous variables will be performed using Mann-Whitney U tests and for categorical variables using Chi-squared or Fisher's exact test, as appropriate. Mean differences and 95% confidence intervals will be presented as a forest plot for subgroup analyses and partial effect plots will be used for continuous variables.

Conclusion: We describe, before the completion of enrollment, our approach to analyzing the data from the CHECK-UP study. We anticipate that this pre-specified framework will enhance the utility of the reported result and allow readers to better judge the impact.

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